228. Total Synthesis of (±)-Clovene. On the Stereoelectronic Requirements of the α-Alkynone Cyclisation

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Summary

The synthesis of the sesquiterpenoid tricyclic hydrocarbon (±)-clovene (**1**) by application of the α-alkynone cyclisation is described. The starting bicyclic carboxylic acid **2** was obtained from ethyl 3-methyl-2-oxocyclohexane-1-carboxylate by modified known methods (24%) and converted to the α-alkynone **3** (86%). The thermolysis of **3** in the gas phase at 620° selectively produced the tricyclo[6.3.1.$0^{1,5}$]dodecenone **4** (80%) which was converted to **1** (37%) by conventional procedures. The selectivity of the α-alkynone cyclisation is discussed in terms of the stereoelectronic requirements (coplanarity factor) of the carbene insertion. In order to throw further light on the importance of this factor, the (1-adamantyl)alkynone **16** was synthesised from adamantane-1-carboxylic acid (78%) and subjected to thermolysis at 620°. Since this led to the tetracyclo[6.3.1.$1^{3,10}$.$0^{3,7}$]tridecenones **17** and **18** (together 72%), we conclude that the planar carbene insertion transition state, while preferred, is not a stringent requirement.

1. Introduction. – Clovene ((–)-**1**), a tricyclic sesquiterpenoid hydrocarbon, is one of the products of the acid-catalysed rearrangement of the natural product caryophyllene[2]). The constitution and configuration of **1** have been established by the work of several groups [2] [4] [5] and confirmed by three syntheses [6–8]. We undertook to synthesise **1** in order to further test the cyclopentenone-annelation sequence **A**→**D** [9], already known to be useful in the synthesis of various polyquinane systems including natural products [10–14]. Since the starting acid **2** of the annelation sequence in our approach was known [15] [16] and since the further transformations of the product **4** of this sequence to (±)-clovene (**1**) involved standard reactions, the success of our synthesis solely depended on the degree of regio- and stereoselectivity of the thermal step **3**→**4**. Consequently, our route serves as a refining test for the previously examined

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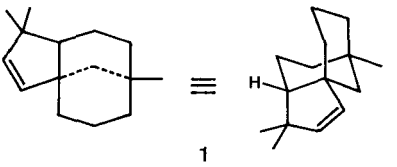
[2]) What today is called 'clovene' is not the compound that *Wallach* originally called 'clovene'. *Wallach* first attributed the name in 1892 [1] to the oily dehydration product of 'a new alcohol' (m.p. 96° = β-caryophyllene alcohol or caryolanol [2]) derived from caryophyllene by acid-catalysed hydration. The same name was later given to the acid-catalysed isomerisation product obtained directly from caryophyllene [3] because the closely similar physical properties available at that time suggested structural identity with *Wallach*'s 'clovene'. Although the non-identity of this and *Wallach*'s hydrocarbon was established by *Lutz & Reid* in 1953 [4], the name 'clovene' was retained for the product obtained directly from caryophyllene.

Scheme 1



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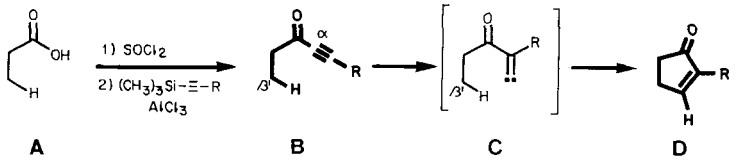
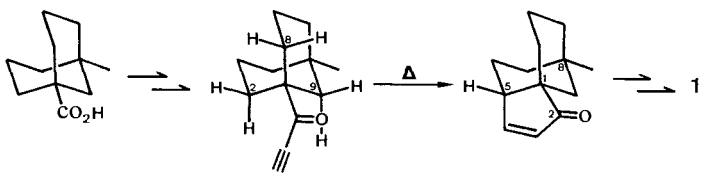


R = H, D, CH_3, $Si(CH_3)_3$

selectivities of the α-alkynone cyclisation [10], according to which the cyclisation **C**→**D** preferentially involves the C(β')-atom of higher substitution, but only if the H,C(β') bond can reach an almost synperiplanar arrangement with the α-alkynone side chain (coplanarity factor). In **3**, all three C(β')-atoms C(2), C(8), and C(9) are of the same degree of substitution, so that the product formation depends primarily on the coplanarity factor. The range of mobility of the ring system of **3** predicts that only the *'exo'*-situated H-atoms at C(2) and C(8) can satisfy that factor, namely in the boat forms of the cyclohexane moieties. Thus, the coplanarity factor was expected to favour the desired product **4**.

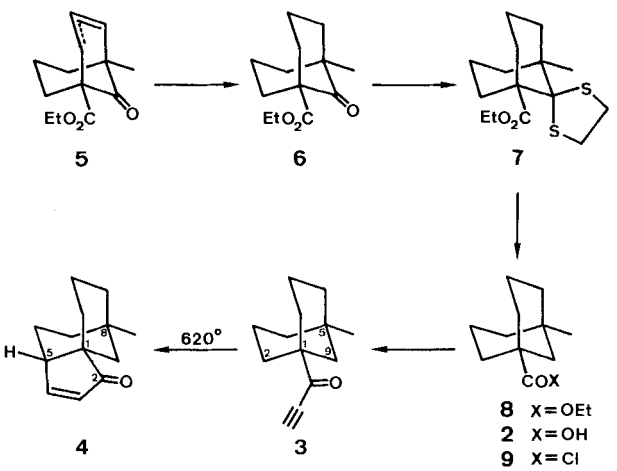
Scheme 2



2 3 4

2. Synthesis and Thermolysis of Ethynyl 5-Methylbicyclo[3.3.1]non-1-yl Ketone (3). – Our synthesis of the known bicyclic acid **2** from ethyl 3-methyl-2-oxocyclohexane-1-carboxylate followed *Raphael*'s procedure [16] with the following modification of the sequence **5**→**2** *(Scheme 3)* as used by *Wiseman* [17] for a lower homologue: Hydrogenation of **5** (mixture of the Δ^2- and Δ^3-isomers, *cf.* [18]), followed by ethylenedithioacetal formation with $BF_3 \cdot Et_2O$ [19] provided **7** (92% from **5**). Desulfurisation with *Raney*-Ni [17] afforded the ester **8** (98%) which was saponified to the acid **2** (93%). The α-alkynone **3** (2-fold symmetry of the bicyclic substructure) finally resulted from the acylation of bis(trimethylsilyl)acetylene with the acyl chloride **9** [9] and hydrodesilylation of the crude β-trimethylsilyl-alkynone intermediate as in [11] (86% from **2**).

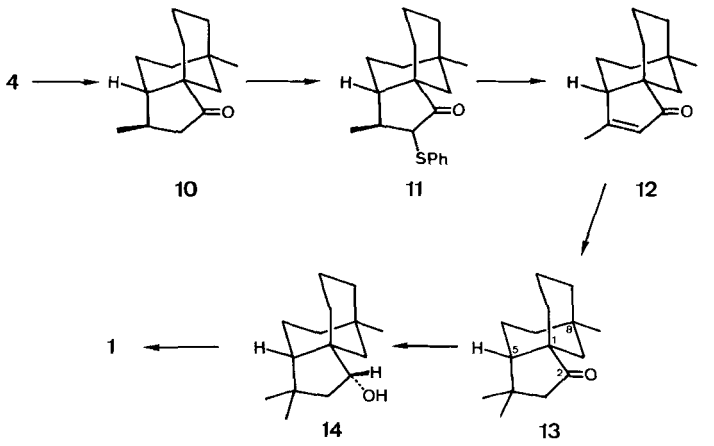
Scheme 3



The thermolysis of **3** was performed by passing gaseous **3** in a stream of N_2 at reduced pressure through a hot quartz tube filled with quartz chips at 620° (*cf.* [9]). The product consisted to the extend of more than 90% of one component (GC and ^{1}H-NMR), suggesting a high degree of regio- and stereoselectivity for the thermal step (see below). Although the 2-cyclopentenone moiety of this major component was readily recognised, the remaining constitution and the configuration of the tricyclic system could not be derived from its spectral data. The identification of the thermolysis product as **4** (80%) was achieved by the subsequent synthetic steps. We also attempted to identify the preferred conformation of the cyclohexane moieties in **3** and of the cyclohexane moiety fused to the 2-cyclopentenone ring in **4** by ^{13}C-NMR using the data of [20], but a conclusion was not immediately evident.

3. Synthesis of (±)-Clovene (1). – The conversion of the 2-cyclopentenone moiety of **4** to the dimethylcyclopentene unit of (±)-clovene (**1**) is summarised in *Scheme 4*. Dimethylcuprate addition to **4** afforded one stereoisomer **10** (91%), presumably the one with the CH_3-group at C(4) *cis* to H–C(5), since the reagent is expected to attack from the less hindered side of the 5-membered ring. Regeneration of the C(3),C(4) double bond by sulfenylation (to **11**), oxidation, and thermal elimination (method of [21]) afforded the β-methylated enone **12** (62% from **10**). Although **11** was found to be one stereoisomer, its relative configuration could not be reliably deduced. Addition of the second CH_3-group to C(4) of **12** provided the racemic form of the known [22–24] perfume ingredient clovanone (**13**; 98%). The C(2),C(3) double bond was introduced by $LiAlH_4$ reduction of **13** to (±)-clovanol (**14**; 96%) [22] [23] followed by dehydration to the target (±)-clovene (**1**; 70%). The IR and ^{1}H-NMR spectra of **1** were identical to those of (–)-clovene, which we had prepared by the acid treatment of caryophyllene according to [4][2]); the mass spectrum of **1** was found to be comparable to those reported in [7] [25].

Scheme 4



4. Synthesis and Thermolysis of the Adamantyl-alkynone 16. – In order to test the requirement of the synperiplanar transition state **C** for the α-alkynone cyclisation, the adamantyl-alkynone **16** was subjected to thermolysis. The 6 equivalent H,C(β') bonds available for insertion in **16** are all *trans* to the alkynone side chain with respect to one of the cyclohexane rings; they all form a dihedral angle of 60° with the reactive side chain and, due to the rigidity of the ring system, are unable to attain the synperiplanar arrangement. The α-alkynone **16** (3-fold symmetry of the tricyclic substructure) was obtained by conversion of adamantane-1-carboxylic acid to the acyl chloride **15** as described in [26], followed by acylation of bis(trimethylsilyl)acetylene under *Friedel-Crafts* conditions at −78° (low temp. to prevent decarbonylation, *cf.* [27]) and hydrodesilylation (method of [11]) of the crude β-trimethylsilyl-alkynone (99% from **15**).

The results of different thermolyses of **16** performed as described above for **3** are shown in the *Table*. At 620°, the product was mainly **17**, accompanied by its double bond rearrangement product **18**, a compound with C_s-symmetry, and starting material **16**. At 650°, no **16** was recovered and at 700°, the more stable symmetric isomer **18** was the major product. That **18** was indeed a rearrangement product of **17** was shown by subjecting isolated **17** to further thermolyses (see *Table*), which produced more **18** (GC, ^{1}H-NMR) with increased temperature.

In addition to providing a total synthesis of (±)-clovene (**1**) and a convenient method for the attachment of a cyclopentenone ring to the adamantane skeleton (*cf.* [28] [29]), our results extend the knowledge of the directing effects in the α-alkynone cycli-

Scheme 5

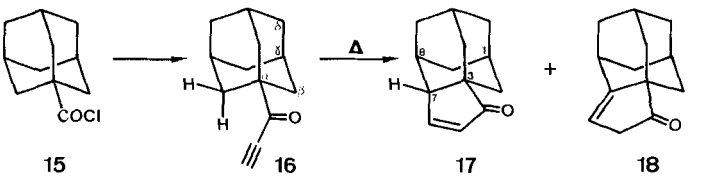


Table. *Thermolyses of* **16** *and* **17**

Starting material	Thermolysis temp. [°C]	GC Ratio (isolated yield [%]) of products		
		16	**17**	**18**
16	620	10 (20)	81 (51)	9 (8)
	650	–	79 (34)	21 (9)
	700	–	38 (18)	62 (24)
17	650	–	79	21
	700	–	57	32

sation. The high selectivity in the thermal step **3**→**4** confirms that the ability of the five C-atoms involved to reach a coplanar conformation (such as in **C**) is a distinct advantage (*cf.* [10]); the conversion of **16** to the tetracycle **17**, however, shows that a certain deviation from this coplanarity can be tolerated by the α-alkynone cyclisation.

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Experimental Part

1. *General.* See [10].

2. *Ethyl 5-Methyl-9-oxobicyclo[3.3.1]nonan-1-carboxylate* (**6**). Hydrogenation of a solution of 5.89 g (25.2 mmol; purity *ca.* 95%) of **5** (obtained as in [16]) in 50 ml of EtOH in the presence of 60 mg of 10% Pd/C for 89 h (method of [17], monitored by anal. GC (*SE-52*, 150°)), filtration through *Celite*, and evaporation yielded, after bulb-to-bulb distillation at 130°/0.02 Torr, 5.68 g (97%; purity 96% by anal. GC) of **6** as a clear, colourless oil. An anal. sample was obtained by column chromatography (silica gel, hexane/AcOEt 95:5) and bulb-to-bulb distillation. IR (film): 2960*s*, 2930*s*, 2870*m*, 1730*s* (CO_2Et), 1710*s* (C=O), 1450*m*, 1380*m*, 1365*m*, 1295*m*, 1250*s*, 1225*s*, 1170*m*, 1140*s*, 1105*m*, 1025*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.22 (*q*, *J* = 7.2, 2H, CH_3CH_2O); 2.68–2.46 (*m*, 2H); 2.34–1.92 (*m*, 6H); 1.90–1.50 (*m*, 4H); 1.29 (*t*, *J* = 7.1, 3H, CH_3CH_2O); 1.00 (*s*, 3H, CH_3–C(5)). ^{13}C-NMR (25,2 MHz, $CDCl_3$): 215.2 (*s*, C=O); 172.4 (*s*, CO_2Et); 60.7 (*t*); 58.4 (*s*); 46.0 (*s*); 41.4 (*t*); 36.2 (*t*); 24.5 (*q*); 20.2 (*t*); 14.0 (*q*). MS (70 eV): 224 (25, M^+), 196 (9), 182 (30), 155 (34), 123 (69), 81 (100), 67 (68), 55 (49), 41 (68), 39 (54). Anal. calc. for $C_{13}H_{20}O_3$ (224.29): C 69.61, H 8.99; found: C 68.96, H 8.78.

3. *(Ethyl 5-Methylbicyclo[3.3.1]nonane-1-carboxylate)-9-spiro-2'-(1',3'-dithiolane)* (**7**). To a stirred solution of 6.99 g (28.1 mmol; purity *ca.* 90%) of **6** and 4.48 g (47.6 mmol) of ethanedithiol in 120 ml of CH_2Cl_2 was added, at r.t., 1 ml of $BF_3 \cdot Et_2O$ (method of [19]). A 2-ml portion of $BF_3 \cdot Et_2O$ was added every 24 h (a total of 7 ml) until **6** had reacted (90 h, monitored by anal. GC (*SE-52*, 200°)). The mixture was washed with 70 ml of 5% NaOH/H_2O, with H_2O, and with brine and dried ($MgSO_4$). After removal of the solvent and bulb-to-bulb distillation of the excess ethanedithiol at 140°/14 Torr, the residual oil solidified on cooling to afford 9.01 g (94%; purity 88% by anal. GC) of **7** as a white solid. An anal. sample was obtained as white needles by recrystallisation from hexane, m.p. 68.6–69.9°. IR (paraffin oil): 2950*s*, 2920*s*, 2860*s*, 1735*s* (C=O), 1455*s*, 1375*m*, 1275*m*, 1240*s*, 1205*s*, 1115*s*, 1060*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.11 (*q*, *J* = 7.1, 2H, CH_3CH_2O); 3.16 (*s*, 4H, $S(CH_2)_2S$); 2.68–2.44 (*m*, 2H); 2.26–1.84 (*m*, 6H); 1.74–1.52 (*m*, 4H); 1.26 (*t*, *J* = 7.1, 3H, CH_3CH_2O); 1.10 (*s*, 3H, CH_3–C(5)). MS (70 eV): 300 (19, M^+), 241 (7), 227 (6), 207 (10), 145 (10), 133 (39), 105 (100), 91 (19), 55 (16), 41 (27). Anal. calc. for $C_{15}H_{24}O_2S_2$ (300.46): C 59.96, H 8.05, S 21.34; found: C 59.99, H 8.24, S 21.07.

4. *Ethyl 5-Methylbicyclo[3.3.1]nonane-1-carboxylate* (**8**). A solution of 9.65 g (28.3 mmol; purity *ca.* 88%) of **7** in 200 ml of EtOH was added (method of [17]) with stirring to 200 g of wet *Raney*-Ni (*Fluka AG*, Buchs, CH) suspended in 100 ml of EtOH and stirred under reflux for 2.5 h. The mixture was allowed to cool to r.t. and filtered through *Celite*, the filter cake being washed with EtOH. Concentration of the filtrate and bulb-to-bulb distillation of the residual oil at 130°/0.8 Torr yielded 5.85 g (98%; pure by anal. GC (*SE-52*, 120°)) of **8** as a clear, colourless oil. An anal. sample was obtained by column chromatography (silica gel, hexane/AcOEt 97.5:2.5) and bulb-to-bulb distillation. IR (film): 2940*s*, 1725*s* (C=O), 1455*m*, 1365*m*, 1245*s*, 1215*m*, 1185*m*,

1125*s*, 1070*m*, 1035*m*, 970*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.10 (*q*, *J* = 7.2, 2H, CH_3CH_2O); 2.10–1.40 (*m*, 12H); 1.44–1.10 (*m*, 2H); 1.24 (*t*, *J* = 7.2, 3H, CH_3CH_2O); 0.87 (*s*, 3H, CH_3–C(5)). GC/MS (*SE-54*, 150°, 70 eV): 210 (3, M^+), 137 (16), 95 (8), 88 (4), 81 (13), 70 (6), 61 (9), 45 (15), 43 (100). Anal. calc. for $C_{13}H_{22}O_2$ (210.31): C 74.24, H 10.55; found: C 74.26, H 10.73.

5. *5-Methylbicyclo[3.3.1]nonane-1-carboxylic Acid* (**2**). A mixture of 5.55 g (26.4 mmol) of **8**, 100 ml of 25% KOH/H_2O, and 70 ml of MeOH was heated to reflux for 2 h. After cooling and acidification with 6N HCl to pH 1, the white precipitate was taken up in Et_2O and dried ($MgSO_4$). Removal of the solvent afforded 4.46 g (93%; pure by anal. GC (*SE-52*, 120°)) of **2** as a white solid, m.p. *ca.* 132°; recrystallised from hexane, m.p. 139.1–142.4° ([16]: m.p. 141–143°). IR (paraffin oil): 3300–2500 (br.), 1710*s* (C=O), 1460*s*, 1410*m*, 1380*m*, 1330*m*, 1285*s*, 1265*m*, 905*m*, 720*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 11.48 (br. *s*, 1H, OH); 2.10–1.44 (*m*, 12H); 1.36–1.12 (*m*, 2H); 0.88 (*s*, 3H, CH_3–C(5)). ^{13}C-NMR (25.2 MHz, $CDCl_3$): 185.3 (*s*, C=O); 43.1 (*t*); 42.8 (*s*); 37.6 (*t*); 33.1 (*q*); 32.6 (*t*); 30.3 (*s*); 22.2 (*t*).

6. *5-Methylbicyclo[3.3.1]nonane-1-carbonyl Chloride* (**9**). A solution of 4.46 g (24.5 mmol) of **2** in 19 ml of $SOCl_2$ was heated to reflux for 1 h according to [30]. Removal of the excess $SOCl_2$ by distillation followed by bulb-to-bulb distillation of the residue at 130°/0.7 Torr yielded 4.64 g (95%; pure by anal. GC (*SE-52*, 120°)) of **9** as a clear, colourless oil. IR (film): 3000*m*, 2950*s*, 2850*s*, 1795*s* (C=O), 1490*m*, 1460*m*, 1225*m*, 1155*m*, 1045*m*, 1015*s*, 970*m*, 910*m*, 880*s*, 775*s*, 760*m*, 725*s*, 705*s*, 695*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.20–1.16 (*m*, 14H); 0.92 (*s*, 3H, CH_3–C(5)). MS (70 eV): 137 (79, $M^+ - COCl$), 95 (73), 81 (100), 67 (34), 55 (21), 41 (34). Anal. calc. for $C_{11}H_{17}ClO$ (200.70): C 65.83, H 8.54, Cl 17.66; found: C 65.53, H 8.77, Cl 17.50.

7. *Ethynyl 5-Methylbicyclo[3.3.1]non-1-yl Ketone* (**3**). Treatment of 4.64 g (23.1 mmol) of **9** with bis(trimethylsilyl)acetylene (method of [11]) gave, after bulb-to-bulb distillation at 130°/0.02 Torr, 6.06 g of the (trimethylsilyl)alkynone as a pale yellow oil which upon hydro-desilylation [11] and bulb-to-bulb distillation at 80°/0.01 Torr yielded 4.01 g (86% from **2**; pure by anal. GC (*SE-52*, 150°)) of **3** as a clear, colourless oil. UV (EtOH): 211 (5300). IR (film): 3300*m*, 3250*s* (H–C≡), 2995*m*, 2960*s*, 2920*s*, 2850*s*, 2095*s* (C≡C), 1665*s* (C=O), 1485*m*, 1460*s*, 1230*s*, 1160*s*, 1100*s*, 1060*m*, 1035*m*, 965*m*, 930*s*, 690*m*, 640*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.23 (*s*, 1H, H–C≡); 2.16–1.16 (*m*, 12H); 1.43 (*s*, 2H, $H_2C(9)$); 0.91 (*s*, 3H, CH_3–C(5)). ^{13}C-NMR (25.5 MHz, $CDCl_3$): 193.5 (*s*, C=O); 80.0 (*d*); 79.8 (*s*); 48.7 (*s*); 42.3 (*t*); 37.6 (*t*); 33.0 (*q*); 31.4 (*t*); 30.4 (*s*); 22.0 (*t*). GC/MS (*SE-54*, 160°, 70 eV): 190 (1, M^+), 147 (2), 137 (100), 95 (55), 81 (93), 67 (19), 59 (15), 55 (15), 45 (16), 41 (17). Anal. calc. for $C_{13}H_{18}O$ (190.27): C 82.06, H 9.54; found: C 81.97, H 9.47.

8. *(1RS,5RS,8SR)-8-Methyltricyclo[6.3.1.0^{1,5}]dodec-3-en-2-one* (**4**). The thermolysis of 505 mg (2.66 mmol) of **3** at 620°/14 Torr for 1 h was carried out in the apparatus described in [9]. Bulb-to-bulb distillation at 85°/0.04 Torr of the crude product yielded 446 mg of a mixture which contained 91% of **4** (by anal. GC (*SE-52*, 150°)), yield 80%, and 9% of 4 other components isomeric with **4** (by GC/MS (*SE-54*, 150°)) as a pale yellow semisolid. An anal. sample of **4** was obtained by column chromatography (silica gel, hexane/AcOEt 95:5) and recrystallisation from hexane, white microcrystals, m.p. 41.9–43.6°. UV (EtOH): 222 (10000), 271 (1300). IR (film): 3060*m*, 3040*m*, 2920*s*, 2860*s*, 1700*s* (C=O), 1585*m* (C=C), 1460*m*, 1350*m*, 1240*m*, 1210*m*, 845*s*, 830*m*, 760*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.56 (*dd*, *J* = 5.7, 2.5, 1H, H–C(4)); 6.14 (*dd*, *J* = 5.7, 1.9, 1H, H–C(3)); 2.54 (*ddt*, *J* = 13, 6, 2, 1H, H–C(5)); 2.90–1.00 (*m*, 12H); 0.96 (*s*, 3H, CH_3–C(8)). ^{13}C-NMR (25.2 MHz, $CDCl_3$): 214.0 (*s*, C=O); 165.8 (*d*); 131.1 (*d*); 47.5 (*s*); 47.0 (*d*); 39.8 (*t*); 38.5 (*t*); 33.3 (*t*); 32.3 (*q*); 31.8 (*t*); 29.4 (*s*); 24.4 (*t*); 19.6 (*t*). GC/MS (*SE-54*, 150°, 70 eV): 190 (100, M^+), 175 (11), 161 (24), 147 (78), 133 (19), 120 (14), 108 (22), 91 (36), 77 (23), 65 (13), 55 (26), 39 (35). Anal. calc. for $C_{13}H_{18}O$ (190.27); C 82.06, H 9.54; found: C 82.24, H 9.28.

9. *(1RS,4SR,5RS,8SR)-4,8-Dimethylbicyclo[6.3.1.0^{1,5}]dodecan-2-one* (**10**). To a stirred suspension of 1.02 g (5.4 mmol) of CuI in 9 ml of Et_2O at −10° was added dropwise 6 ml of 1.6M MeLi in Et_2O, keeping the temp. below −5°. A solution of 276 mg (1.29 mmol; purity *ca.* 89%) of **4** in 2 ml of Et_2O was added dropwise at *ca.* −20°. The mixture was allowed to warm up to 0° within 20 min, stirred at 0° for 1 h, cooled to −60°, and treated with 1.5 g of solid NH_4Cl at once and then with 15 ml of H_2O and 15 ml of conc. NH_4OH. After stirring at r.t. for 30 min, the phases were separated, and the aq. phase was extracted 6 times with 10-ml portions of Et_2O. The combined Et_2O extracts were washed with H_2O, and brine, then dried ($MgSO_4$) and evaporated. Bulb-to-bulb distillation at 90°/0.01 Torr afforded 278 mg (91%; purity 87% by anal. GC (*SE-52*, 150°)) of **10** as a pale yellow oil. IR (film): 2950*s*, 2920*s*, 2870*s*, 1730*s* (C=O), 1460*s*, 1405*m*, 1380*m*, 1270*m*, 1230*m*, 1180*m*, 1170*m*, 1115*m*, 1065*m*, 990*m*, 980*m*, 730*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.56 (*dd*, *J* = 18.3, 7.4, 1H, H–C(3)); 2.20–0.85 (*m*, 15H); 1.09 (*d*, *J* = 6.3, 3H, CH_3–C(4)); 0.89 (*s*, 3H, CH_3–C(8)). GC/MS (*SE-54*, 150°, 70 eV): 206 (100, M^+), 191 (15), 177 (6), 163 (15), 149 (9), 136 (35), 121 (32), 108 (26), 95 (30), 81 (34), 69 (28), 55 (30), 41 (56). Anal. calc. for $C_{14}H_{22}O$ (206.32): C 81.50, H 10.75; found: C 81.16, H 10.50.

10. *(1RS,4RS,5RS,8SR)-4,8-Dimethyl-3-phenylthiotricyclo[6.3.1.0^{1,5}]dodecan-2-one* (**11**). A solution of lithium diisopropylamide (1.65 mmol) in THF was prepared according to [31] and used in the sulfenylation of 170 mg (0.72 mmol; purity *ca.* 87%) of **10** (method of [21]). Purification by column chromatography (silica gel, hexane/AcOEt 97.5:2.5) gave 216 mg (96%; pure by anal. GC (*SE-52*, 200°)) of **11** as a white solid. An anal. sample was obtained by recrystallisation from pentane as colourless rhombic crystals, m.p. 61–63°. UV (EtOH): 202 (12800), 216 (sh, 8800), 248 (3200). IR (film): 3050*m*, 2950*s*, 2920*s*, 2860*s*, 1735*s* (C=O), 1585*m*, 1480*m*, 1460*s*, 1440*m*, 1375*m*, 1165*m*, 745*s*, 735*s*, 690*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.55–7.50 (*m*, 2H); 7.31–7.26 (*m*, 3H); 2.98 (*d*, J = 10.9, 1H, H–C(3)); 2.06–0.80 (*m*, 14H); 1.22 (*d*, J = 6.3, 3H, CH_3–C(4)); 0.70 (*s*, 3H, CH_3–C(8)). GC/MS (*SE-54*, 200°, 70 eV): 314 (92, M^+), 248 (8), 205 (21), 189 (8), 177 (7), 163 (9), 150 (100), 135 (17), 121 (25), 107 (15), 95 (31), 81 (43), 69 (46), 55 (30), 41 (76). Anal. calc. for $C_{20}H_{26}OS$ (314.47): C 76.38, H 8.33, S 10.20; found: C 76.30, H 7.94, S 10.32.

11. *(1RS,5RS,8SR)-4,8-Dimethyltricyclo[6.3.1.0^{1,5}]dodec-3-en-2-one* (**12**). Oxidation of 3.46 g (11.0 mmol) of non-recrystallised **11** was carried out with *m*-chloroperbenzoic acid in CH_2Cl_2 using the method of [21]. A solution of the resulting crude phenylsulfoxide in 85 ml of toluene was refluxed with 1.10 g (11.0 mmol) of $CaCO_3$ for 4 h (*cf.* [21]), TLC (silica gel, hexane/AcOEt 75:25, $Ce(SO_4)_2$) being used to monitor the reaction progress. Filtration of the suspension and removal of the solvent gave a brown oil which on bulb-to-bulb distillation at 130°/0.01 Torr, column chromatography (silica gel, hexane/AcOEt 9:1), and a final bulb-to-bulb distillation at 110°/0.03 Torr yielded 1.43 g (64% from **11**; pure by anal. GC (*SE-52*, 150°)) of **12** as a clear, colourless oil which solidified on cooling. An anal. sample was obtained by recrystallisation from pentane (cooling) as microcrystals, m.p. 50.8–52.3. UV (EtOH): 229 (13200). IR (film): 3060*w*, 2920*s*, 2860*s*, 1690*s* (C=O), 1620*s* (C=C), 1455*m*, 1435*m*, 1375*m*, 1315*m*, 1265*m*, 1205*m*, 1065*m*, 855*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.78 (*q*, J = 1.1, 1H, H–C(3)); 2.25 (*dd*, J = 13, 6, 1H, H–C(5)); 2.07 (*d*, J = 1.1, 3H, CH_3–C(4)); 1.84–1.0 (*m*, 12H); 0.93 (*s*, 3H, CH_3–C(8)). GC/MS (*SE-54*, 150°, 70 eV): 204 (100, M^+), 189 (18), 176 (20), 161 (59), 147 (11), 134 (11), 122 (23), 108 (19), 91 (22), 79 (16), 67 (18), 51 (10), 41 (39). Anal. calc. for $C_{14}H_{20}O$ (204.30): C 82.30, H 9.87; found: C 82.06, H 9.68.

12. *(1RS,5RS,8SR)-4,4,8-Trimethyltricyclo[6.3.1.0^{1,5}]dodecan-2-one (= (±)-Clovanone;* **13**). Methylation of 1.30 g (6.4 mmol) of **12** as described above for **4** yielded, after bulb-to-bulb distillation at 110°/0.01 Torr ([23]: b.p. 96–97°/0.5 Torr), 1.37 g (98%; pure by anal. GC (*SE-52*, 150°)) of **13** as a clear, colourless oil. IR, ^{1}H-NMR, MS: identical with those in [23].

13. *(1RS,2SR,5RS,8SR)-4,4,8-Trimethyl[6.3.1.0^{1,5}]dodecan-2-ol (= (±)-Clovanol;* **14**). Reduction of 470 mg (2.05 mmol; purity *ca.* 96%) of **13** with $LiAlH_4$ (method of [7]) gave 436 mg (96%; pure by anal. GC (*SE-52*, 160°)) of **14** as a clear, colourless oil that solidified on standing. Sublimation at 140°/12 Torr afforded fine white needles, m.p. 57–60° ([22] for (–)-**14**: 97–98.5°). IR (film): 3600–3100*s* (br., OH), 2970*s*, 2860*s*, 1450*m*, 1360*m*, 1065*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.82 (*dd*, J = 9.7, 6.5, 1H, H–C(2)); 1.80–0.70 (*m*, 16H); 0.97 (*s*, 6H); 0.90 (*s*, 3H) (*cf.* [22]). MS (70 eV): 222 (12, M^+), 204 (4), 189 (10), 180 (9), 166 (100), 161 (5), 149 (4), 135 (16), 123 (25), 107 (8), 95 (18), 85 (25), 81 (21), 67 (9), 55 (13).

14. *(1RS,5RS,8SR)-4,4,8-Trimethyl[6.3.1.0^{1,5}]dodec-2-ene (= (±)-Clovene;* **1**). After dropwise addition of 8 ml of $POCl_3$ to a vigorously stirred solution of 377 mg (1.70 mmol) of sublimed **14** in 4 ml of pyridine cooled in an ice-bath, the mixture was heated to reflux for 1 h. Workup (method of [32]) and bulb-to-bulb distillation of the crude product at 150°/14 Torr ([7]: b.p. 80°/0.15 Torr) afforded 243 mg (70%; purity 97% by anal. GC (*SE-52*, 150°)) of **1** as a clear, colourless oil. IR, ^{1}H-NMR: identical with those of (–)-**1** (see *Exper. 15*). MS: in agreement with those in [7] [25].

15. *(–)-Clovene* ((–)-**1**) *by Acid-Catalysed Rearrangement of Caryophyllene.* Acid treatment of 4.33 g (21.2 mmol) of caryophyllene (*Fluka AG*, Buchs, CH), as described in [4], purification by column chromatography (silica gel, hexane), and bulb-to-bulb distillation at 150°/14 Torr yielded (–)-**1**. IR (film): 3030*m*, 2940*s*, 2920*s*, 2860*s*, 2845*s*, 1460*s*, 1360*m*, 965*w*, 905*w*, 875*w*, 800*w*, 770*m*, 760*m*. (*cf.* [7] for IR (CCl_4)). ^{1}H-NMR (200 MHz, $CDCl_3$): 5.36 (*d*, J = 5.6, 1H, H–C=); 5.28 (*d*, J = 5.6, 1H, H–C=); 1.80–0.80 (*m*, 13H); 1.05 (*s*, 3H); 0.95 (*s*, 3H); 0.86 (*s*, 3H).

16. *Ethynyl Adamant-1-yl Ketone (= Ethynyl Tricyclo[3.3.1.1^{3,7}]decyl Ketone;* **16**). To a stirred suspension of 373 mg (2.79 mmol) of $AlCl_3$ in 3 ml of CH_2Cl_2 at –78° was added dropwise within 20 min a solution of 523 mg (2.26 mmol; purity *ca.* 86%) of adamantane-1-carbonyl chloride (**15**; prepared from adamantane-1-carboxylic acid (*Fluka AG*, Buchs, CH) in 79% yield as described in [26]) and 561 mg (3.30 mmol) of bis(trimethylsilyl)acetylene in 3 ml of CH_2Cl_2. The mixture was allowed to warm to –20° within 1.25 h, treated with 8 ml of 4% HCl/H_2O, vigorously stirred, and extracted 4 times with 4 ml portions of hexane. Washing of the combined org. extracts with brine, drying ($MgSO_4$), and removal of the solvent afforded a yellow/brown semisolid which was bulb-to-bulb distilled at 180°/0.01 Torr. The product was hydro-desilylated by the method of [11] to give

420 mg (99% from **15**; pure by anal. GC (*SE-52*, 160°)) of **16** as a white solid, m.p. 100–105°. An anal. sample was obtained by recrystallisation from hexane as colourless needles, m.p. 105.2–105.5°. UV (EtOH): 212 (5600). IR (paraffin oil): 3250*s* (H–C≡), 2905*s*, 2855*s*, 2090*s* (C≡C), 1665*s* (C=O), 1455*m*, 1210*m*, 1170*m*, 1020*s*, 750*m*, 700*m*, 690*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.22 (*s*, 1H, H–C≡); 2.08 (br. *s*, 3H, 3H–C(γ)); 1.90 (br. *s*, 6H, $3H_2C(\beta)$); 1.74 (br. *s*, 6H, $3H_2C(\delta)$) (*cf.* [33]). GC/MS (*SE-54*, 160°, 70 eV): 188 (1, M^+), 135 (100), 107 (11), 93 (33), 79 (42), 67 (13), 55 (11), 41 (18). Anal. calc. for $C_{13}H_{16}O$ (188.26): C 82.93, H 8.57; found: C 82.66, H 8.81.

17. *Thermolysis of* **16**. The thermolysis of 58 mg (0.31 mmol) of **16** at 620°/14 Torr for 45 min was carried out in the apparatus described in [9] to afford a crude product containing *tetracyclo[6.3.1.1^{3,10}.0^{3,7}]tridec-5-en-4-one* (**17**), *tetracyclo[6.3.1.1^{3,10}.0^{3,7}]tridec-6-en-4-one* (**18**), and recovered **16** in a ratio of 81:9:10 (anal. GC (*SE-52*, 160°)). Separation by column chromatography (silica gel, hexane/AcOEt 95:5) and subsequent bulb-to-bulb distillation gave 29 mg (51%, 63% based on non-recovered **16**) of **17**, 4.4 mg (8%; 9% based on non-recovered **16**) of **18**, and 11.6 mg (20%) of **16**.

17: White semisolid, b.p. 110°/0.01 Torr. UV (EtOH): 233 (6900). IR (paraffin oil): 3115*w*, 3080*w*, 3055*w*, 2910*s*, 2850*s*, 1705*s* (C=O), 1560*m* (C=C), 1450*s*, 1335*s*, 1195*m*, 1105*m*, 1015*m*, 985*m*, 910*s*, 840*m*, 785*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.55 (*ddd*, J = 5.7, 1.8, 0.7, 1H, H–C(6)); 6.05 (*dd*, J = 6.0, 3.2, 1H, H–C(5)); 2.90 (br. *s*, 1H, H–C(7)); 2.31–1.57 (*m*, 13H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 212.7 (*s*, C=O); 161.9 (*d*); 131.5 (*d*); 53.4 (*d*); 49.8 (*s*); 39.2 (*t*); 39.1 (*t*); 37.0 (*t*); 35.2 (*t*); 32.6 (*t*); 30.5 (*d*); 28.4 (*d*); 27.8 (*d*). GC/MS (*SE-54*, 160°, 70 eV): 188 (62, M^+), 160 (100), 145 (22), 131 (18), 117 (84), 108 (49), 91 (58), 80 (53), 65 (23), 53 (15), 39 (37). Anal. calc. for $C_{13}H_{16}O$ (188.26): C 82.93, H 8.57; found: C 82.72, H 8.51.

18: b.p. 80°/0.01 Torr, m.p. 71–73°. UV (EtOH): 200 (4600). IR (paraffin oil): 2910*s*, 2850*s*, 1745*s*/1730*s* (C=O), 1660*m* (C=C), 1450*s*, 1265*m*, 1215*m*, 1175*m*, 1040*m*, 975*m*, 815*m*, 790*s*, 715*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.45 (*t*, J = 2.0, 1H, H–C(6)); 2.90 (*d*, J = 2.0, 2H, $H_2C(5)$); 2.72 (*t*, J = 2.8, 1H, H–C(8)); 2.20–1.5 (*m*, 12H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 221.5 (*s*, C=O); 152.9 (*s*); 108.8 (*d*); 51.2 (*s*); 41.9 (*t*); 38.9 (*t*); 38.0 (*t*); 36.4 (*t*); 34.3 (*d*); 28.6 (*d*). GC/MS (*SE-54*, 160°, 70 eV): 188 (54, M^+), 160 (100), 145 (10), 131 (29), 117 (98), 105 (22), 91 (84), 77 (20), 65 (21), 53 (13), 41 (35). Anal. calc. for $C_{13}H_{16}O$ (188.26): C 82.93, H 8.57; found: C 82.67, H 8.83.

The thermolysis of 285 mg (1.51 mmol) of **16** at 650°/14 Torr as above gave 161 mg of crude **17**/**18** in a ratio of 79:21 (anal. GC (*SE-52*, 160°)). Purification as described above afforded 97 mg (34%) of **17** and 25 mg (9%) of **18**.

The thermolysis of 475 mg (2.52 mmol) of **16** at 700°/14 Torr as above gave 321 mg of crude **17**/**18** in a ratio of 38:62 (anal. GC (*SE-52*, 160°)). Purification as described above afforded 86 mg (18%) of **17** and 114 mg (24%) of **18**.

18. *Thermolysis of* **17**. The thermolysis of 21 mg (0.11 mmol) of **17** at 650°/14 Torr as described above gave 17 mg (80%) of a 79:21 mixture **17**/**18**. The thermolysis of 23 mg (0.12 mmol) of **17** at 700°/14 Torr gave 14 mg (63%) of a 57:32 mixture **17**/**18** (anal. GC (*SE-52*, 160°) and ^{1}H-NMR (200 MHz)).

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